REMARKS

I. Preliminary Comments and Amendments to the Specification

Applicants note, with gratitude, the withdrawal of the previous rejections and the entry of the amendment correcting the obvious typographical error.

Applicants hereby amend independent claim 6 in accordance with the suggestion of the Examiner to delete the recitation of "correlating said change in expression level, mutation or rearrangement with a standard indicative of a hyperproliferative disease to determine the occurrence of a hyperproliferative disease" and recite in its place "wherein said change in expression level, mutation or rearrangement is indicative of hyperproliferative disease." No new matter is introduced by this amendment, and it is submitted that the amendment places the claims in condition for allowance.

II. Subject Matter of the Invention

The present application relates to the discovery that the ELP protein is a tumor suppressor (see page 6, lines 3-30, and Example X, page 35, lines 1-30), and that alterations in expression levels of ELP, mutations in the nucleic acid sequence encoding an ELP protein, or rearrangements in the genomic *elp* locus correlate with altered tumor suppressor activity and, consequently, with hyperproliferative diseases or a predisposition thereof. (*See* page 9, line 31 – page 11, line 9). In addition, Applicants have provided methods of analyzing samples of subjects to identify abnormalities in ELP, either in protein or mRNA expression or in mutations of the DNA sequence, as a means of identifying a hyperproliferative disease. (*See* Example XI, page 35, line 33 – page 36, line 22).

III. Outstanding Rejections

Claims 6-12 stand rejected under 35 U.S.C. §112, first paragraph, for lack of written description.

Claims 6-12 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement with respect to detection in body fluid samples.

IV. Patentability Arguments

A. Rejection of Claims 6-12 under 35 U.S.C. §112, First Paragraph (written description).

The rejection of claims 6-12 for lack of written description/new matter should be withdrawn in light of the amendment of independent claim 6 to delete the recitation of "correlating said change in expression level, mutation or rearrangement with a standard indicative of a hyperproliferative disease to determine the occurrence of a hyperproliferative disease" and substitution in its place of the language "wherein said change in expression level, mutation or rearrangement is indicative of hyperproliferative disease" as suggested by the Examiner. No new matter is introduced thereby, and it is submitted that the rejection for lack or written description/new matter for the language previously submitted may be withdrawn.

B. Rejection of Claims 6-12 under 35 U.S.C. §112, First Paragraph (enablement).

Applicants note, with appreciation, the withdrawal of the previous rejections (including rejections for lack of enablement) and the acknowledgement by the Examiner at page 4 of the Action that the disclosure is "enabling for a method of the identification of a hyperproliferative disease, which comprises detecting a change in ELP mRNA or protein expression levels from a tissue sample..."

Applicants submit that their disclosure also enables those of ordinary skill in the art to practice the method of identification of a hyperproliferative disease in a body fluid. While the specification provides no examples for measuring *Elp* gene sequence or expression at the RNA or protein levels in bodily fluids, such methods were well known in the art and are expected to function according to Applicants' invention. Not only does the scientific literature show that the analysis of bodily fluids for the diagnosis of non-hematopoetic tumors was well accepted but the specific concerns voiced in the Action that the tumor cell antigen expression might be down-regulated or lost are misplaced.

The art teaches that cells disseminate from non-haematopoetic tumors and can be found in serum and bone marrow as well as other bodily fluids. There were (and are) numerous publications confirming the presence and the validity of the detection of tumor

cells in bodily fluids. Such cells can obviously resist for a long time and can be the cause of a spreading of the cancer through formation of metastasis. Two examples of such publications impressively demonstrate the presence of disseminated cells from non-haematopoetic tumors in the bodily fluids:

Kasimir-Bauer et al., 2001: This group investigated the presence of disseminated breast cancer cells even after high-dose chemotherapy and indeed such cells could be found in the bone marrow.

Lauschke et al., 2001: This group investigated the presence of mutations in the oncogene K-ras and the tumor suppressor gene APC in *serum* DNA of colon cancer patients. Whereas, K-ras (oncogene) mutations were difficult to find in serum, APC (tumor suppressor gene) mutations were detected in 80% (20/25) in the serum of patients with APC mutations in the primary tumor. Beside this significant result, the group could detect the presence of mutant DNA in the serum 10 days after surgical removal of the tumor which led them to conclude that cells or at least mutant DNA of disseminated cells are not rapidly cleared from the blood.

Submitted herewith is the Declaration of Barbara Froesch, Ph.D. (Exhibit 1) stating that it was well established at the time of applicants' invention that analysis of bodily fluids was a reliable measure to diagnose tumors. A review of the scientific literature demonstrates that the analysis of bodily fluids such as saliva, serum, urine, peritoneal fluid and bone marrow for DNA and other markers could be used for the diagnosis of non-haematopoetic tumors like lung, renal and gastric cancers as set out in the publications below:

Publication	**Set-up**	**Result**
Hibi et al., "Molecular Detection of Genetic Alternations in the Serum of Colofectal Cancer Patients," *Cancer Research* 58: 1405-1407 (1998)	Microsatellite analysis of genetic alterations in **serum DNA** obtained from 44 **colorectal cancer** patients.	"Taken together, either a K-*ras* or p*53* mutation was detected in the serum in 40% of the 25 patients (95% confidence interval, 21-61%), whose primary tumors contained a mutation and in 23% of the 44 patients (95% confidence interval 12-38%) with colorectal cancer. The frequent detection of *p53*

		mutation in the serum of patients with early stage tumor suggests a possible use of this approach for clinical prognosis and cancer monitoring of colorectal cancer patients."
El-Naggar et al., "Genetic heterogeneity in saliva from patients with oral squamous carcinomas:implications in molecular diagnosis and screening," *J Mol Diagn.* 3(4):164-70 (2001).	Microsatellite analysis of **head and neck squamous carcinoma** (HNSC) on **saliva** and matched tumors in 37 patients.	-"epithelial cells in saliva[...]provide suitable material for genetic analysis" -in 49% of patients genetic alterations (LOH) could be detected in saliva
Spafford et al., "Detection of head and neck squamous cell carcinoma among exfoliated oral mucosal cells by microsatellite analysis," *Clin Cancer Res.* 7(3):607-12 (2001).	Microsatellite analysis of **saliva** in **head and neck squamous cell carcinoma** (HNSCC) patients.	Microsatellite instability was detected in 96% and LOH in 61% of cases with corresponding genetic alterations in the primary tumors.
Lauschke et al., "Detection of APC and k-ras mutations in the serum of patients with colorectal cancer," *Cancer Detect Prev.* 25(1):55-61 (2001).	Detection of K-ras and APC mutations in **serum DNA** of **colon** cancer patients.	K-ras mutations only found in the serum of 6/22 patients but APC mutations found in serum of 20/25 patients
Schott et al., "Isolated tumor cells are frequently detectable in the peritoneal cavity of gastric and colorectal cancer patients and serve as a new prognostic marker," *Ann Surg.* 227(3):372-9 (1998).	**Bone marrow** or **peritoneal cavity fluid** of **gastric** or **colorectal** patients were investigated immunocytochemically.	Little prognostic significance of positive bone marrow results but high correlation of results from peritoneal cavity fluid and survival rate.

Kersting et al., "Differential frequencies of p16(INK4a) promoter hypermethylation, p53 mutation, and K-ras mutation in exfoliative material mark the development of lung cancer in symptomatic chronic smokers," *J Clin Oncol.* 18(18):3221-9 (2000).	**Sputum** analysis in **lung cancer** patients for p53, K-ras and p16.	Differences on DNA level could be detected in 14-51% of patients if the markers were analyzed individually but in 69% if the markers were combined.
Eisenberger et al., Diagnosis of renal cancer by molecular urinalysis," *J Natl Cancer Inst.* 91(23): 2028-32 (1999).	Microsatellite alterations in **urine** and **serum** of **renal cancer** patients.	Alterations could be found in 76% of urine samples and 60% of serum samples.
Vogel et al., "Disseminated tumor cells in pancreatic cancer patients detected by immunocytology: a new prognostic factor," *Clin Cancer Res.* 5(3):593-9 (1999).	Immunocytochemical analysis of **peritoneal cavity fluid** and **bone marrow** in **pancreatic cancer** patients.	In 39 and 38% of patients alterations could be found in peritoneal lavage or bone marrow, respectively. Combination of the two bodily fluids resulted in 52% of correctly diagnosed patients.
Weitz et al.,"Detection of disseminated colorectal cancer cells in lymph nodes, blood and bone marrow," *Clin Cancer Res.* 5(7):1830-6 (1999).	Expression analysis of CK by RT-PCR on **lymph nodes** (lymphatic system), **blood** and **bone marrow** samples of **colon cancer** patients.	CK detection in lymph nodes is of prognostic relevance.
Chang et al., "Molecular diagnosis of primary liver cancer by microsatellite DNA analysis in the serum," *Br J Cancer.* 87(12): 1449-53 (2002).	Analysis for LOH in **serum** of **liver cancer** patients.	LOH found in 76.2% of patients.

Hickey et al., "Molecular detection of tumour DNA in serum and peritoneal fluid from ovarian cancer patients," *Br J Cancer* 80(11):1803-8 (1999).	Analysis of genetic alterations in **serum** and **peritoneal fluid** of **ovarian cancer** patients.	In 17/20 serum samples and 12/19 peritoneal fluid samples, genetic alterations could be detected.
A. Vogel et al., "Disseminated tumor cells. Their detection and significance for prognosis of gastrointestinal and pancreatic carcinomas" *Virchows Arch.* 439(2): 109-17 (2001).	Review of the various **methods to detect disseminated tumor cells** used at the time and the prognostic relevance of the results gained from these studies.	"Our evaluation of the studies on colorectal, gastric and pancreatic ductal carcinomas indicates that detection of disseminated tumor cells in different compartments may lead to more accurate tumor staging."

These publications show that analysis of bodily fluids for the diagnosis of non-haematopoetic tumors was well accepted in the art at the time of applicants' invention because disseminated tumor cells or DNA of non-haematopoetic tumor cells could be found in nearly all bodily fluids (e.g., serum, saliva, bone marrow, peritoneal cavity fluid, sputum, urine, lymph nodes, and blood, as noted in the above publications). While negative results exist they depend upon the marker/antigen/genetic alteration that is investigated. A striking example for this is the low significance in diagnosing colorectal cancer by the detection of mutations of the oncogene K-ras in comparison to mutation in the tumor suppressor genes APC or *p53* (see Lauschke et al. and Hibi et al.).

Tumor diagnosis by the analysis of bodily fluids is well accepted and state of the art at the time of applicants' invention. Low performance of certain methods is rather due to poor marker quality and/or tool selectivity (e.g. antibodies) rather than to the method as such. The present invention helps to solve this problem because it introduces a new tumor marker which is significantly downregulated in certain tumors. In addition, in contrast to many other tumor markers (like PSA), the biological function of Elp as tumor suppressor has been shown experimentally (in the disclosure of the specification, at, for example, Example XI at page 35, line 33 – page 36, line 22). Consequently, Elp has already undergone validation as a diagnostic tumor marker.

The enablement rejection on the basis that a protein might not be expressed in the tumor and therefore might not represent a reliable tumor marker does not apply to the present invention which relies upon the widely used method of detecting tumorogenic mutations/rearrangements within the nucleic acid sequence of a tumor suppressor gene like *elp*. The argument that antigen-levels in body fluids are difficult to measure because they are lost or downregulated does not apply for Elp and the present invention because Elp is a tumor suppressor and therefore (already) lost or downregulated in the primary tumor. In the case of Elp, it is therefore very useful as one aspect of the invention to detect mutations of Elp or genomic rearrangements of the Elp locus in disseminated cells which is independent of how reliably one can detect Elp antigen levels.

The reference in the Official Action to Vogel et al. *Virchows Arch* 439:109-117 (2001) (hereafter "Vogel et al.") for the proposition that antigen levels in bodily fluids are hard to measure is said to be supported by Klein et al., who isolated single disseminated cells from bone marrow of a breast cancer patient. An examination of this reference shows, however, that various genetic analyses on those cells comes to a conclusive result despite variances between the single isolated cells (see entire document or last sentence of abstract). They also clearly state that the reliability and variability of such analyses strongly depend on the marker/antigen and the available tools, e.g. antibodies, but less on the methods *per se*. The reviewer further suggests that the problem could be overcome by the parallel use of multiple markers. Thus, the present invention improves the significance of such analyses and therefore aims to solve the problem by the use of an additional tumor marker.

Cells of Non-Haematopoetic Tumors are Present in a Variety of Bodily Fluids

The argument in the Official Action that Vogel et al. (referring to p.110 par 7) teach that "**disseminated tumor cells** of non-haematopoetic origin normally do not circulate in the peripheral blood" is incorrect. Specifically, the Official Action misinterprets the sentence in the review, which cites:

> "When disseminated tumour cells are analysed using RNA-based assays for epithelial cells, it has to be assumed that **cells of non-haematopoetic origin** normally do not circulate in the peripheral blood or one marrow."

The fact that only tumor and not normal non-haematopoetic cells circulate into the peripheral blood or bone marrow represents the prerequisite for the predictive value of such measurements. Otherwise, detection of non-haematopietic cells in bodily fluids could not necessarily be linked to the presence of a tumor. This, however, is not a condition *sine qua non,* as it is only important if the marker *per se* is not tumor specific but primarily a marker for tissue origin and/or differentially expressed in tumor cells without mutations in its nucleic or amino acid sequences. In the case of elp, tumor cell isolation would only be required if one needed to measure elp expression levels, whereas detection of mutations or rearrangements in the elp nucleic acid or protein sequence can directly be investigated without prior isolation of circulating tumor cells, particularly, for instance, of the lung, kidney and stomach. Thus, in case of a tumor suppressor, detection of a mutated nucleic acid or protein sequence in the blood would strongly indicate to a person skilled in the art the presence of a tumor, independently of the concomitant occurrence of tumor cells in the blood.

The state of the art, as outlined in the appended declaration by Dr. Froesch and as summarized in the above table, shows that various cancers have been correlated to a range of markers in bodily fluids. In some cases, the marker is intracellular (e.g., tumor cells from a tissue sample or extracted from a saliva sample), while in other cases, the marker is extracellular (e.g., serum or urine analysis of circulating DNA or protein). The identification of a mutation of the isolated DNA or alteration of expression level of an ELP protein will occur in a similar manner and via means well known in the art, regardless of whether the source of that isolated DNA or ELP protein was intracellular, extracellular, or via a tissue sample.

In conclusion, analysis of body fluids for changes in the expression level of ELP proteins, or mutations within the nucleic acid sequence encoding an ELP protein or detecting a rearrangement in the genomic elp locus was well within the skill of the art given the teachings of the specification and the enablement rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

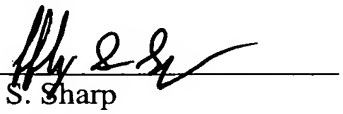
V. Conclusion

In view of the above amendment and remarks, applicants believe the pending application is in condition for allowance. Should the Examiner wish to discuss any issues of

form or substance in order to expedite allowance of the pending application, he is invited to contact the undersigned attorney at the number indicated below.

Dated: August 15, 2006

Respectfully submitted,

By 

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